matter has been added. Applicant respectfully requests reconsideration and allowance of the present application.

I. SEQUENCE LISTING:

Applicant provides herewith a paper copy and computer readable copy of the sequence listing for the present application in accordance with 37 C.F.R. 1.821 et seq.

II. DRAWINGS:

Applicant respectfully requests deferment of the filing of formal drawings until, and at such time, as Applicant receives a Notice of Allowance.

Applicant submits that the drawings comply with 37 C.F.R. §1.83(a).

III. SPECIFICATION:

The Office Action objects to the disclosure because the "Brief Description of the Drawings" allegedly does not reflect the claim language. Applicant respectfully submits that the description of the drawings reflects the pending claim language.

The specification (including the Examples) has been amended throughout to correct typographical mistakes and to clarify abbreviations based upon their first use in the description.

The Office Action alleges that the specification fails to provide proper antecedent basis for the claimed subject matter. In particular, the Office Action alleges that the specification fails to describe or mention "extremophiles", "thermophiles, hyperthermophiles, psychrophiles, and psychrotrophs". Applicant respectfully directs the Examiner to page 16, lines 9-11 which recite these terms.

IV. REJECTION UNDER 35 U.S.C. §112, FIRST PARAGRAPH

with gene expression of a reporter gene as the basis of the detectable signal in the specification.

allegedly does not reasonably provide enablement for performing the method in a cell with a non-gene expression based detectable signal or for performing the method *in vitro* with either type of detectable signal. Applicant respectfully traverses this rejection.

The Office Action alleges that the present specification does not enable a non-gene based detectable signal. Applicant respectfully reminds the Examiner that a patent need not teach, and preferably omits, what is well known in the art. *In re Buchner*, 929 F.2d 660, 661, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991); *Spectra-Physics, Inc. v. Coherent, Inc.*, 827 F.2d 1524, 3 USPQ2d 1737 (Fed. Cir. 1987); *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986), *cert. denied*, 480 U.S. 947 (1987); and *Lindemann Maschinenfabrik GMBH v. American Hoist & Derrick Co.*, 730 F.2d 1452, 1463, 221 USPQ 481, 489 (Fed. Cir. 1984). All that is necessary is that one skilled in the art be able to practice the claimed invention, given the level of knowledge and skill in the art.

In vitro gene expression systems or "cell-free" systems have been known for over a decade. Accordingly, one skilled in that art would be able to perform the methods of the present invention in a cell-free system based upon teaching known to those of skill in the art at the time the present application was filed and based upon the teachings provided in the present specification.

In addition, non-gene based detectable signals were known in the art at the time of filing the present application. The specification teaches the quenching effect and fluorescence effect of GFP molecules in close proximity (pages 34-35). One of skill in the art would recognize from the present teaching that rather than utilizing a gene based reporter system, the association (or lack thereof) of two hybrid proteins (*i.e.*, a first protein with a first fluorescent molecule, and a second protein with a second fluorescent molecule) can be monitored due to fluorescent

are associated, there is a quenching of the fluorescent wavelength and the detector

fluorescent wavelength. The changes in wavelengths can be monitored by standard optical methods. Accordingly, Applicant respectfully requests withdrawal of the §112, first paragraph, rejection.

Claims 45-47 stand rejected under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention without undue experimentation. The Office Action alleges that claims 45-47 have additional method steps which have no clear connection to the steps preceding A-F and succeeding steps (i)-(ii). While Applicant respectfully traverses this rejection, claims 45-47 have been amended to clarify the relationship of the method based on the sub-numbering. Accordingly, Applicant respectfully requests withdrawal of the rejection.

V. REJECTION UNDER 35 U.S.C. §112, SECOND PARAGRAPH

Claims 16-47 stand rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Applicant respectfully traverses this rejection.

The Office Action alleges that claim 16 is indefinite because the terms "interaction of a first hybrid protein and second hybrid protein" and "wherein interaction of the first protein and second protein" appear to be different interactions that need to be clarified. Applicant has amended claim 16 to claim the invention with better particularity and therefore respectfully requests withdrawal of the §112, second paragraph, rejection.

The Office Action alleges that claim 17 is indefinite because of the phrase, "the

[illegible] rejection of claim [illegible] under [illegible] second paragraph [illegible]

Claim 36 is allegedly indefinite for recitation of "in the absence . . . of a detectable response". As the Examiner correctly stated, the phrase is meant to refer to the "off" or "negative" state of a binary signal response (*e.g.*, repression of gene expression). However, in contrast to the Examiner's statement that claim 36 is "essentially a duplicate of claim 16", Applicant respectfully submits that claims 16 and 36 are not duplicative but claim the subject matter of the present invention in patentably different ways (e.g. claim 36 includes a contacting element not recited in claim 16). Accordingly, Applicant respectfully requests withdrawal of the §112, second paragraph, rejection.

Claims 22-25 and 38-40 stand rejected under 35 U.S.C. §112, second paragraph, as allegedly incomplete for omitting essential steps. The Office Action alleges that the omitted steps are "expression of the first, second and third recombinant genes in the host cell which is requisite for the method to succeed." (Office Action at page 8, paragraph 16.) Applicant respectfully traverses this rejection.

Applicant respectfully submits that the rejected claims do not omit an essential step. For example, claims 38-40 recite providing a first, second or third gene expressed in the host cell. Accordingly, Applicant respectfully requests withdrawal of the §112, second paragraph, rejection.

Claims 45-47 stand rejected as allegedly indefinite for recitation of additional method steps which are not explicitly related to the method steps cited in claims on which they are dependent. Applicant respectfully traverses this rejection.

Claim 45-47 have been amended to clarify the relationship of the sub-numbering recited in the claims. Accordingly, Applicant respectfully requests withdrawal of the §112,

VI. REJECTION UNDER 35 U.S.C. §102

Claims 16-26 and 36-42 stand rejected under 35 U.S.C. §102 as allegedly anticipated by U.S. Patent No. 5,525,490 to Erickson *et al.* Applicant respectfully traverses this rejection.

Erickson *et al.* allegedly discloses a method for identifying a molecule which modulates the interaction between at least a first and second protein. Erickson *et al.*, does not teach or suggest a molecule from a library generated from a mixed population of organisms as recited in Applicant's claims 16 and 36, upon which the remaining claims depend. Erickson *et al.* fails to teach or suggest each and every element of Applicant's invention. Accordingly, Applicant respectfully requests withdrawal of the §102 rejection.

Claims 16-17, 20, 22, 23, 24, and 36-39 stand rejected under 35 U.S.C. §102 as allegedly anticipated by U.S. Patent No. 5,322,801 to Kingston *et al.* Applicant respectfully traverses this rejection.

Kingston *et al.* allegedly discloses a method for identifying a molecule which modulates the interaction between at least a first and second protein. Kingston *et al.*, does not teach or suggest a molecule from a library generated from a mixed population of organisms as recited in Applicant's claims 16 and 36, upon which the remaining claims depend. Kingston *et al.* cannot anticipate Applicant's claimed invention because Kingston *et al.* fails to teach or suggest each and every element of Applicant's invention. Accordingly, Applicant respectfully requests withdrawal of the §102 rejection.

VII. REJECTION UNDER 35 U.S.C. §103

Claims 16-26 and 36-42 stand rejected under 35 U.S.C. §103(a) as allegedly unpatentable over either Erickson *et al.* or Kingston *et al.* in view of Mendelsohn *et al.* (Curr. Op. in Biotech. 1994 5:482-486). Applicant respectfully traverses this rejection.

Neither Erickson *et al.* nor Kingston *et al.* teach or suggest the claimed invention, as discussed above. Mendelsohn *et al.* also does not teach a molecule from a library made from a mixed population of organisms as recited in Applicant's claims 16 and 36. Thus, even if there were some suggestion to combine Mendelsohn *et al.* with Erickson *et al.* and/or Kingston *et al.*, which there is not, the combination of references does not teach or suggest the use of such a library as a source of DNA in the method of the claimed invention. Accordingly, Applicant respectfully requests withdrawal of the §103(a) rejection.

Claims 16-45 stand rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Erickson *et al.* in view Stein *et al.* (1996 J. Bact. 178:591-599) and Horikoshi (1995 Curr. Op. in Biotech. 6:292-297). Applicant respectfully traverses this rejection.

Applicant respectfully submits that the Office Action has failed to set forth a *prima facie* case of obviousness. In the absence of Applicant's disclosure, there must be found, at the time of filing, motivation or teaching to combine the cited references. In this case, there is no such motivation outside the disclosure of Applicant's invention. The alleged teaching is found, not in the references, but in the claims being rejected. It is error to reconstruct the claimed invention from the prior art by using the rejected claim as a "blueprint." *Interconnect Planning Corp. v. Feil*, 227 USPQ 543, 548 (Fed. Cir. 1985).

population of organisms, wherein the molecule either directly or indirectly [illegible]

protein interactions, for example. Stein *et al.* allegedly teaches creating libraries from uncultivated marine microorganisms. Stein *et al.* does not teach or suggest identifying proteins or molecules that modulate protein-protein interactions. Horikoshi allegedly teaches enriching populations of extremophiles for prokaryotic organisms. Horikoshi does not teach or suggest identifying proteins or molecules that modulate protein-protein interactions. The combination of the foregoing references fails to provide any motivation or reason, and thus provide the claimed method, to mixed population libraries for molecules that can modulate protein-protein interactions. Applicant respectfully submits that the present rejection is based upon hindsight reconstruction of Applicant's invention based upon a number of references that do not teach or suggest the combination. Accordingly, Applicant respectfully requests withdrawal of the §103(a) rejection.

Claims 16-33 and 36-45 stand rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Erickson *et al.* in view of Short *et al.* (WO 97/04077) and Horikoshi. Applicant respectfully traverses this rejection.

Erickson *et al.* has been discussed above. Short *et al.* is cumulative to Stein *et al.* above, and allegedly teach creating libraries from uncultivated microorganisms. These references do not teach or suggest identifying proteins or molecules that modulate protein-protein interactions. Horikoshi allegedly teaches enriching populations of extremophiles for prokaryotic organisms. Horikoshi does not teach or suggest identifying proteins or molecules that modulate protein-protein interactions. The combination of the foregoing references fails to provide any motivation or reason, and thus provide the claimed method, for searching or examining mixed population libraries for molecules that can modulate protein-protein interactions. Applicant respectfully submits that the present rejection is based upon hindsight reconstruction of Applicant's invention

Claims 16-47 stand rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Erickson *et al.* in view of Stein *et al.* and Horikoshi, as applied to claims 16-45, and further in view of Patanjali *et al.* Applicant respectfully traverses this rejection.

Applicant respectfully submits that the Office Action has failed to set forth a *prima facie* case of obviousness. There is no suggestion, teaching, or motivation to arrive at Applicant's invention of identifying molecules in a library made from a mixed population of organisms that modulate interacting molecules. As discussed above, Erickson *et al.* fails to teach or suggest the claimed invention. Stein *et al.* allegedly teaches creating libraries from uncultivated marine microorganisms. Stein *et al.* does not teach or suggest identifying proteins or molecules that modulate protein-protein interactions. Horikoshi allegedly teaches enriching populations of extremophiles for prokaryotic organisms but does not teach or suggest identifying proteins or molecules that modulate protein-protein interactions. Patanjuli *et al.* is combined with the foregoing references to allegedly teach normalization of cDNA. The addition of Patanjuli *et al.* does not remedy the deficiencies of the prior references and thus does not provide a *prima facie* case of obviousness. The combination of the foregoing references fails to teach the claimed invention. Applicant respectfully submits that the present rejection is based upon hindsight reconstruction of Applicant's invention based upon a number of references that do not teach or suggest the combination. Accordingly, Applicant respectfully requests withdrawal of the §103(a) rejection.

In view of the above remarks, reconsideration and favorable action on all claims is respectfully requested.

Respectfully submitted,

Date: 5/6/01

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EXHIBIT A

VERSION OF CLAIMS WITH MARKINGS

16. (Amended) A method for identifying a DNA sequence [molecule] which encodes a molecule or molecules which directly or indirectly modulate[s] the interaction between at least a first and second [protein] molecule, comprising:

introducing into a cell containing interacting molecules which generate or repress a detectable signal or growth of the cell, genomic DNA or clones of a DNA library generated from nucleic acid derived from a mixed population of organisms and measuring the interaction of a first [hybrid protein] interacting molecule and a second [hybrid protein] interacting molecule in the presence of a [test] third molecule encoded by the library or the genomic DNA or produced as a result of expression of one or more products encoded by the library or the genomic DNA, wherein [the first hybrid protein comprises a first domain and the first protein and the second hybrid protein comprises a second domain and the second protein, wherein] interaction of the first [protein] and the second [protein causes] molecules in the absence of the third molecule produces a detectable [response] signal or growth of the cell; [and]

comparing the [detectable response] signal or growth of the cell in the presence and absence of the [test molecule] genomic DNA or library, wherein a difference between the response[s] or growth is indicative of [a test] the presence of a molecule that modulates [protein-protein] interaction between the first and second molecules; and

identifying a clone or DNA sequence which encodes a molecule or molecules which directly or indirectly modulates the interaction between the first and second molecules.

17. (Amended) The method of claim 16, wherein [the first domain is] at least one of the interacting molecules contains a DNA-binding moiety and [the second domain is] at least one of

EXHIBIT A

19. (Amended) The method of claim 17, wherein the DNA-binding moiety and the transcriptional activation moiety are derived from [a] different proteins.

20. (Amended) The method of claim [17] 16, wherein the detectable signal is produced from a gene [encodes] encoding a protein selected from the group consisting of β-galactosidase, green fluorescent protein, luciferase, alkaline phosphatase and [chloramphenical] chloramphenicol acetyl transferase.

22. (Amended) The method of claim [17] 16, wherein the detectable signal is encoded by a gene [is] present in a host cell.

23. (Amended) The method of claim 22, wherein the host cell further comprises a first recombinant gene encoding the first [hybrid protein] molecule, a second recombinant gene encoding the second [hybrid protein] molecule, or a third recombinant gene encoding the [test] third molecule, wherein the first, second or third gene are expressed in the host cell.

25. (Amended) The method of claim 23, wherein the host cell contains the first, second and third genes.

27. (Amended) The method of claim 16, wherein the [test molecules] library is derived from an environmental [library] sample.

29. (Amended) The method of claim [27] 16 or 28, wherein the environmental library is derived from an environmental sample comprising uncultured microorganisms.

EXHIBIT A

33. (Amended) The method of claim [27] 16 or [28] 23, wherein the library is created by obtaining an environmental sample, enriching the environmental sample for [prokaryotic] eukaryotic organisms and selecting against [eukaryotic] prokaryotic organisms, isolating nucleic acids from the enriched sample, fractionating the nucleic acids, and cloning the isolated nucleic acids into a vector.

36. (Amended) A method for [detecting the ability of] identifying a molecule [to] that affects the interaction between a first and second [protein] molecule, comprising:

(i) contacting a first [hybrid protein] molecule with a second [hybrid protein] molecule in the presence of [the test] a third molecule derived from a library made from a mixed population of organisms or in the presence of the library or genomic DNA [, the first hybrid protein comprising:

(a) a first domain and the first protein; and

the second hybrid protein comprising:

(b) a second domain and the second protein;]

wherein association of the first and second [hybrid proteins] molecules in the absence of the [test] third molecule results in the absence or presence of a detectable response by changing expression of a detectable gene or detectable gene product; and

(ii) comparing the detectable response in the presence of the [test] third molecule with the detectable response in the absence of the [test] third molecule, wherein a difference in response is indicative of the presence of a molecule that affects the interaction between a first and second molecule.

EXHIBIT A

38. (Amended) The method of claim 37, further comprising, prior to (i):
[(A)] providing a prokaryotic host cell containing the detectable gene; and
[(B)] providing a first gene [capable of being] expressed in the host cell, the first gene encoding the first [hybrid protein] molecule.

39. (Amended) The method of claim 38, further comprising, prior to (i):
[(C)] providing a second gene [capable of being] expressed in the host cell, the second gene encoding the second [hybrid protein] molecule.

40. (Amended) The method of claim 39, further comprising, prior to (i):
[(D)] providing a third gene [capable of being] expressed in the host cell, the third gene encoding the [test] third molecule.

41. (Amended) The method of claim 40, further comprising, prior to (i):
[(E)] introducing said first, second and third genes into the host cell; and
[(F)] allowing expression of the genes.

42. (Amended) The method of claim [41] 36, wherein the [first domain is] molecule contains a DNA binding domain and [the second domain is] a transcriptional activation domain.

43. (Amended) The method of claim [41] 36, wherein the [first and second domains form] interaction between the first and second molecules forms a transcriptional repressor.

44. (Amended) The method of claim [41] 36, wherein the third gene is derived from an

EXHIBIT A

45. (Amended) The method of claim [44] 36, further comprising, prior to (i):

[(G)] obtaining an environmental sample; and

[(H)] enriching the sample for prokaryotic organisms [and selecting against eukaryotic organisms].

46. (Amended) The method of claim 45, further comprising producing a normalized library, comprising [, prior to (i)]:

[(I)] isolating nucleic acids from said enriched environmental sample;

[(J)] fractionating the isolated nucleic acids;

[(K)] melting the recovered fractions and allowing subsequent reannealing; and

[(L)] amplifying any single-stranded nucleic acids present in the sample.

47. (Amended) The method of claim 46, further comprising generating an expression library, comprising [, prior to (i)]:

[(M)] inserting isolated nucleic acids [resulting from (I) or (L)] into an expression vector.

48. (New) A method for identifying a molecule that affects the interaction between a first and second molecule, comprising:

(i) contacting a first molecule with a second molecule wherein at least one of the first or second molecules are derived from a library made from a mixed population of organisms, wherein association of the first and second molecules in the presence of an unidentified molecule results in the presence of a detectable response by changing expression of a detectable gene or detectable gene product; and

(ii) comparing the detectable response in the presence of the inidentified molecule and the first and second molecules with the detectable response in the absence of the unidentified